Predictive Factors for Corneal Infiltrates With Continuous Wear of Silicone Hydrogel Contact Lenses

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Objective: To estimate the cumulative probability and risk factors for developing corneal infiltrates after up to 3 years of continuous wear (CW) with lotrafilcon A lenses.

Methods: Patients were fitted with lotrafilcon A lenses and followed up for 3 years. The main outcome variable was the first occurrence of any infiltrative event in either eye. Cox proportional hazards regression was used to model the probability of developing infiltrates as a function of demographic and biomicroscopy findings.

Results: A total of 317 patients participated in this study. The Kaplan-Meier unadjusted cumulative incidence of a corneal infiltrate after CW was 5.7% (95% confidence interval [CI], 3.0%-8.4%) at the end of 1 year, 8.5% (95% CI, 6.6%-13.9%) at the end of 3 years. Corneal staining and limbal redness present in the affected eye on a previous visit were significantly associated with the development of an infiltrative event (hazard ratios, 7.23 and 3.18; P<.001 and P=.02, respectively).

Conclusions: Corneal staining and limbal redness may predict the subsequent development of an infiltrative event among CW contact lens patients. The probability of remaining free of any corneal infiltrates at the end of 3 years of CW of contact lenses was 89.7% (95% CI, 86.1%-93.4%).

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ORNEAL INFILTRATES HAVE been reported to occur in approximately 1.6% to 4% of non–contact lens–wearing eyes, although most of these are asymptomatic and classified as subepithelial microinfiltrates.1,2 Overnight contact lens use has long been associated with an increased risk of infiltrates.3,4 In extended wear with low-oxygen permeable contact lenses, younger age, higher socioeconomic status, smoking, and bacterial colonization of lenses are other known risk factors.5-10 Disposable (compared with conventional) low-oxygen permeable contact lenses have even been implicated as a risk factor for infiltrates,2,11 although confounding effects of lens material, professional prescribing patterns, and casual patient attitudes may be more responsible than lens modality for the causal effect.

A few studies12-16 have specifically explored the predictive factors for infiltrative events in users of highly oxygen-transmissible silicone hydrogel lenses. Based on a traditional characterization of corneal infiltrative events, which distinguishes between microbial and sterile keratitis,17 risk factors for corneal infiltrative events with continuous wear (CW) of silicone hydrogel lenses include younger age14,16 (especially when combined with smoking),15 male sex,16 blepharitis, bulbar redness, corneal staining,13 and history of previous corneal inflammatory events.13

In a series of recent articles, corneal infiltrative events have been classified as a continuous spectrum of disease severity.12,19-21 These classification schemes for infiltrative events encompass any event that aggregates inflammatory cells in the cornea irrespective of origin and thus include microbial keratitis. According to these scales, the following factors have been associated with development of an infiltrative event in either low-oxygen permeable or silicone hydrogel lenses: overnight use of traditional hydrogel lenses, male sex, smoking, absence of eye and health problems, late winter months, refractive error greater than + or –5.00 diopters (D), failure to achieve a full 30-night wearing period, and younger or older age.

Most previous studies that examined risk factors leading to infiltrative events were based on cross-sectional designs or used statistical techniques relevant to their study design, which could only summarize the failure experiences of subjects at risk by the fraction of subjects who experience an end
point event during the study from among those with complete follow-up. This is an inefficient approach, particularly when time-to-event data are available in an actively followed-up cohort. Patients enrolled in a longitudinal study often are not observed during the entire follow-up period because of removal from the study by the investigator for safety reasons, lack of cooperation in study participation, or migration from the area. Moreover, because subjects are typically enrolled at different points in time, the closing of the study at a fixed time results in differing lengths of follow-up. All of those observations are considered to be censored. In the statistical approaches referred to previously, the experience of those subjects up until the time of discontinuation from the study is ignored. Survival analysis is a class of statistical methods for studying the occurrence and timing of events that allows data from individuals followed up for unequal lengths of time to be fully used. Using data from an existing cohort of 317 patients, we used survival analysis techniques to estimate the cumulative probability and risk factors for developing corneal infiltrates after up to 3 years of CW with lotrafilcon A lenses (Night & Day; CIBA Vision, Duluth, Ga).

Patients were enrolled in a nonrandomized, prospective, open-label longitudinal study across 19 sites in the United States. All patients were bilaterally fit with lotrafilcon A lenses for up to 30 nights of CW and followed up for 3 years. Institutional review board approval was obtained from sites where required. All patients completed informed consent documents, and the study followed the tenets of the Declaration of Helsinki.

The study was intended to simulate day-to-day practice. Patients paid usual and customary fees for examinations and dispensed lenses, and the study sponsor (CIBA Vision Corporation) reimbursed patients for study participation after the completion of follow-up. Neophyte patients suited for extended wear contact lenses, as well as daily wear–experienced contact lens patients, were eligible. Lotrafilcon A lenses were available in either the 8.4- or 8.6-mm baseline curves with powers between +6.00 and −10.00 D.

Scheduled visits included a baseline and dispensing visit, followed by visits at 1 week and 1, 6, 12, 18, 24, and 36 months after dispensing. Unscheduled visits occurred as needed according to patient-reported or eye professional–observed problems. The following baseline variables were recorded and analyzed: date of birth, sex, previous lens-wearing history, preexisting conditions, history of previous contact lens–associated adverse events, smoking status, lens fit, spectacle refraction, and keratometry. Ten different biomicroscopy signs were graded at each visit on the 4-point Efron Grading Scale, including conjunctival redness, limbal redness, corneal neovascularization, epithelial microcysts, corneal edema, corneal staining, conjunctival staining, papillary conjunctivitis, corneal infiltrates, and corneal ulcers.

Patients had to be free of any infiltrative event at baseline to be included in the statistical analysis. One patient had an infiltrate at baseline and thus was excluded from all further analyses. The main outcome variable was the first occurrence of any infiltrative event regardless of slitlamp grade in either eye. If the participant had a bilateral first event, the eye with the more severe infiltrate was used. Therefore, only 1 eye per patient was used in the analysis. Once an eye with an outcome event was reported, the participant was no longer at risk for experiencing that event. A secondary analysis was performed for significant infiltrative events defined as infiltrates of grade 3 or 4 on the Efron Grading Scale.

The Kaplan-Meier product-limit method was used to estimate the cumulative probability of remaining free of significant corneal infiltrates for up to 3 years of CW. We generated Kaplan-Meier plots of estimates of both overall incidence and incidence for patients stratified by covariates found to be significant in subsequent analyses. The log-rank test was used to test for significant differences in the estimates of the cumulative probability of remaining infiltrate free.

Univariate Cox proportional hazards regression was used to assess the statistical significance of each of the potential explanatory factors pertaining to demographics, biomicroscopy findings, manifest refraction, lotrafilcon A lens parameters prescribed, previous contact lens experience, and history of inflammatory events. Biomicroscopy findings analyzed were those seen at the 3 visits immediately preceding the visit during which the infiltrate was noted for those patients who experienced an outcome event and the 3 visits immediately preceding the last visit for those who did not experience the event during their follow-up period. Events were assumed to occur at the time of the closest scheduled visit. Multivariate Cox regression was then used to model the probability of developing infiltrates as a function of relevant demographic characteristics and univariately significant biomicroscopy findings. The assumption of proportionality of hazards in Cox regression was tested by introducing time-dependent covariates.

The correlation between the significant biomicroscopy findings was assessed with the Spearman rank correlation coefficient. All analyses were conducted using SAS statistical software, version 9.0 (SAS Institute Inc, Cary, NC).

A total of 317 patients participated in this study. The mean age of the cohort was 37.8 years, with a range of 12.8 to 71.9 years of age. Males contributed to 33.4% of the sample. Most participants were white (90.9%), followed by African American (4.1%) and Asian (2.5%); 12.3% were smokers. Previous lens modality included 280 participants who were adapted to low-oxygen permeable soft contact lenses; 140 participants were previous daily lens wearers and 140 were previous extended lens wearers. None were previous silicone hydrogel–adapted wearers. Thirty-one patients had not worn contact lenses previously, and 6 were former rigid gas-permeable lens users.

Twenty-seven incident infiltrative events occurred in this cohort during 3 years. Specifically, 16 occurred within the first year, 7 in the second year, and 4 in the third year. The Kaplan-Meier unadjusted cumulative incidence of a corneal infiltrate after CW was 5.7% (95% confidence interval [CI], 3.0%-8.4%) at the end of 1 year, 8.5% (95% CI, 5.2%-11.9%) at the end of 2 years, and 10.3% (95% CI, 6.6%-13.9%) at the end of 3 years. For the subset of significant infiltrates, the unadjusted cumulative incidence of a grade 3 or 4 infiltrative event was 1.8% (95% CI, 0.2%-3.4%) for up to 2 years of CW and 3.1% (95% CI, 0.9%-5.2%) at the end of 3 years.

The Kaplan-Meier plots in Figure 1 and Figure 2 display the unadjusted cumulative probabilities of remaining infiltrate free stratified by the presence or absence of 2 predictor variables, corneal staining and lim-
Participants with corneal staining or limbal redness were significantly less likely \((P < .001)\) to remain infiltrate free compared with participants who ended the study without these clinical slitlamp signs.

Cox proportional hazards modeling was used to estimate the adjusted risk of developing an infiltrate. Variables considered for inclusion in the modeling process were those found to be significant in univariate analyses, as well as demographic variables previously documented to be associated with corneal inflammatory events, specifically age, sex, and smoking status. The final multivariate model is presented in **Table 1**. In this model, corneal staining and limbal redness present in the eye with an infiltrate on a previous visit were significantly associated with elevated hazard ratios for developing an infiltrative event.

For the subset of eyes with significant corneal infiltrates \((n=8)\), no variables were found to be significantly associated with an infiltrative event of grade 3 or 4 on univariate analyses. The final multivariate model was applied to this subset of eyes as well. The trends of elevated risk for corneal staining and limbal redness remained, although the hazard ratios were not statistically significant, presumably because of the small number of events.

Of the 27 participants who had an end point infiltrative event, 63.0\% had some level of corneal staining or limbal redness documented at the last visit before the event. **Table 2** and **Table 3** list the distribution of corneal staining and limbal redness grades for all participants in the study, stratified by outcome. Corneal staining and limbal redness were generally graded as low severity. Of the 17 patients with some level of corneal staining who proceeded to have an end point infiltrate, 15 (88.2\%) were listed as having grade 1 or 2. Of the 17 patients with some level of limbal redness who proceeded to have an end point infiltrate, 14 (82.4\%) were listed as having grade 1 or 2. Furthermore, no correlation was found between the limbal redness and corneal staining grades at the last visit before an infiltrative event \((r = 0.26; P = .20)\).

**Table 1. Multivariate Analysis of Risk Factors for All Corneal Infiltrates**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99 (0.96-1.03)</td>
<td>.97</td>
</tr>
<tr>
<td>Sex</td>
<td>1.61 (0.74-3.49)</td>
<td>.23</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.76 (0.66-4.80)</td>
<td>.26</td>
</tr>
<tr>
<td>Corneal neovascularization</td>
<td>0.54 (0.20-1.41)</td>
<td>.21</td>
</tr>
<tr>
<td>Corneal staining</td>
<td>7.23 (2.93-17.87)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Limbal redness</td>
<td>3.18 (1.22-8.29)</td>
<td>.02</td>
</tr>
</tbody>
</table>

**Table 2. Distribution of Corneal Staining Grades**

<table>
<thead>
<tr>
<th>Corneal Staining Grade</th>
<th>Visit Just Before Infiltrative Event ((n = 27))</th>
<th>Last Visit for Event-Free Participants((n = 284))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10 (37.0)</td>
<td>250 (88.0)</td>
</tr>
<tr>
<td>1</td>
<td>8 (29.6)</td>
<td>25 (8.8)</td>
</tr>
<tr>
<td>2</td>
<td>7 (25.9)</td>
<td>9 (3.2)</td>
</tr>
<tr>
<td>3</td>
<td>1 (3.7)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1 (3.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

\*Percentages may not total 100\% because of rounding.
†Data for 4 participants was not available and for 1 participant was not recorded.

**Table 3. Distribution of Limbal Redness Grades**

<table>
<thead>
<tr>
<th>Limbal Redness Grade</th>
<th>Visit Just Before Infiltrative Event ((n = 27))</th>
<th>Last Visit for Event-Free Participants((n = 284))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10 (37.0)</td>
<td>252 (88.7)</td>
</tr>
<tr>
<td>1</td>
<td>13 (48.1)</td>
<td>31 (10.9)</td>
</tr>
<tr>
<td>2</td>
<td>1 (3.7)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>3</td>
<td>2 (7.4)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1 (3.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

\*Percentages may not total 100\% because of rounding.
†Data for 4 participants was not available and for 1 participant was not recorded.
Most users of lotrafilcon A silicone hydrogel lenses worn for up to 30 nights of CW will remain free of corneal infiltrates after 3 years of use. The probability of remaining free of any corneal infiltrates at the end of 3 years of CW of contact lenses is 89.7% (95% CI, 86.1%-93.4%). The more severe grades, which generally are more symptomatic, interrupt lens wear, and may require intervention, affect significantly fewer people. The probability of remaining free of a grade 3 or 4 infiltrative event at the end of 3 years is 96.9% (94.8%-99.1%).

Only 2 published studies have identified risk factors for the development of corneal infiltrative events associated with extended wear of silicone hydrogel lenses (Table 4). Most factors found to be associated with an infiltrative event by these investigators approximately doubled the risk, except a history of similar complications, which posed a 4 to 7 times greater risk. Additionally, 3 limited reports in published abstracts have cited male sex, younger age, bulbar redness, blepharitis, and corneal staining as risk factors, but no measures of association were provided. Compared with other studies, we found an unusually high relative risk for 2 clinical variables in developing an infiltrate. Limbal redness posed a 3-fold higher risk and corneal staining posed a 7-fold higher risk for the subsequent development of an infiltrative event among 30-night CW contact lens patients in this study. Additionally, we were not able to duplicate elevated relative risks for some previously reported factors, such as history of previous inflammatory events, sex, age, or smoking.

The prospective nature of this study allowed us to identify some novel clinical risk factors present before the development of the infiltrate, establishing temporality between the risk factors and outcome. Theoretically, corneal staining and limbal redness are potentially modifiable; however, they require astute observation by eye professionals during the fitting and follow-up process. Additionally, the identification of these factors provides screening tools for eye professionals as they are selecting the best candidates for CW contact lenses.

Our findings reveal that corneal staining and limbal redness associated with infiltrative events are typically of low severity and most likely asymptomatic. Limbal redness is often a sign of hypoxia in contact lens wear and is usually reduced with silicone hydrogel lens use. The persisting low-grade limbal redness documented in some of these patients may be due to previous use of low-oxygen permeable contact lenses, mechanical irritation, and/or immunological responses. Furthermore, corneal staining and limbal redness are independently associated with the development of infiltrates, and they do not appear to be correlated with one another in this cohort. Corneal staining has been documented in certain lens care systems and silicone hydrogel lens combinations when used for daily wear. In fact, patients in whom contact lens solution had toxic effects during daily wear of soft lenses were shown to be 4 times more likely to experience a corneal infiltrative event than nonaffected controls. In daily wear use of silicone hydrogel lenses with lens care systems, no correlation has been found between corneal staining and limbal redness.

The mechanism of the inflammatory response is largely unknown but may be multifactorial. At least 1 infiltrative event, contact lens peripheral ulcer, has been associated with minor ocular surface trauma, and epithelial injury may precipitate an event. This condition has also been related to transient gram-positive bacterial contamination of the contact lens. Therefore, the mechanism of an inflammatory response related to corneal staining and limbal redness as found in this study may stem from an interplay among subtle epithelial injury, resident or increased bacterial loads, and the release of chemical messengers from the blood supply at the limbus.

In summary, 10 of every 100 wearers of lotrafilcon A lenses worn for up to 30 nights may develop a corneal infiltrative event after 3 years of CW. Other studies have found higher incidence rates than reported herein, but those studies monitored patients monthly or quarterly, which may tend to document higher levels of asymptomatic events because of the frequent visit schedule. In this study, the follow-up visit schedule was set to be consistent with day-to-day practice. Follow-up visits were generally done every 6 months, and all unscheduled visits were included in the analysis. Therefore, the incidence rates determined in this study are likely to be indicative of what would be observed by eye professionals in their own practices, including at unscheduled visits. Many of these infiltrative events are asymptomatic or remain undetected clinically because they are of low severity. Three of every 100 wearers of lotrafilcon A lenses worn for up to 30 nights may develop a significant and/or symptomatic corneal infiltrative event after 3 years of CW. Patients should be screened for low-grade corneal staining and limbal redness, and these findings should be investigated to the fullest extent possible because they may increase the patient's risk of developing a corneal infiltrative event.

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Table 4. Previously Reported Risk Factors for Corneal Infiltrative Events in Silicone Hydrogel Lens Wear12,13

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractive error &gt;=+5.00 D</td>
<td>1.57 (1.11-2.24)</td>
</tr>
<tr>
<td>Wearing time &gt;-21 d</td>
<td>0.48 (0.26-0.89)</td>
</tr>
<tr>
<td>Younger age (&lt;-25 y)</td>
<td>1.65 (1.14-2.39)</td>
</tr>
<tr>
<td>Older age (&gt;50 y)</td>
<td>2.01 (1.29-3.11)</td>
</tr>
<tr>
<td>Age 18-29 y</td>
<td>2.2*</td>
</tr>
<tr>
<td>Smoking and age 18-29 y</td>
<td>2.7*, higher than nonsmokers of same age</td>
</tr>
<tr>
<td>Previous corneal scars</td>
<td>4.1*</td>
</tr>
<tr>
<td>Previous CLARE</td>
<td>6.9*</td>
</tr>
<tr>
<td>Previous infiltrates</td>
<td>6.1*</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CLARE, Contact Lens Acute Red Eye.
*95% CI not available.


**REFERENCES**